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Is Detection of Hibernation Critical in Deciding Surgical Revascularization in Patients with Very Low Ejection Fraction?

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DEFINITION OF HIBERNATING MYOCARDIUM

Myocardial hibernation is a condition of chronic ventricular dysfunction, regional and/or global, due to myocardial ischemia usually due to ischemic heart disease. The term "hibernation" referring to this condition was first coined by Diamond et al. in 1978 [1] but was not widely recognized until Rahimtoola documented the importance of this condition, particularly in relation to potential improvement of ventricular function following myocardial reperfusion therapy [2].

POTENTIAL MECHANISMS

The precise mechanisms of myocardial hibernation have not been established. It has been postulated that it results from subacute or chronic myocardial ischemia resulting from a reduction of coronary blood flow. There is a compensatory concurrent reduction in myocardial oxygen and metabolic demand in the affected myocardial segments. For example, it has been hypothesized that the myocardial contractile function decreases to match the reduction of coronary blood flow. It has been also suggested that hibernation results from repetitive episodes of ischemia/reperfusion resulting from an imbalance between myocardial metabolic demand and oxygen supply, which cannot increase appropriately due to impaired coronary flow reserve. This imbalance causes repetitive episodes of mechanical dysfunction and eventually hibernating myocardium.

The precise biochemical and cellular mechanisms of myocardial hibernation in humans has not been clarified. In animal models the accumulation of glycogen, alteration of calcium regulation and some extent of cell degeneration have been shown. However, in both animal models and patients with myocardial hibernation, increased expressions of several survival genes have been demonstrated. For example, the inhibitor of apoptosis and cytoprotective heat-shock proteins are significantly up regulated in the hibernating myocardium [3]. The potential mechanisms are illustrated in figure 1.

DETECTION AND DIAGNOSIS IN CLINICAL PRACTICE

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A number of non-invasive techniques are in use for detection of hibernating myocardial segments, including dobutamine echocardiography; thallium-201 imaging; use

Chronic coronary artery disease –Coronary stenosis
Decreased or maintained coronary blood flow at rest.
Decreased metabolism Demand ischemia
Decreased function Chronic stunning
Chronically decreased contractile function
Genomic trigger of cell survival
Proteins of survival (IAP, HSPs)

FIGURE 1. (adapted from reference 3). Hibernation: Survival hypothesis.

of technetium-99m labeled agents; FDG PET and magnetic resonance imaging. All these different imaging modalities have been used rather extensively with the same objective of predicting improvement in regional and global myocardial function, in symptoms of heart failure and quality of life and in prognosis.

PREDICTION OF RECOVERY OF REGIONAL FUNCTION

DOBUTAMINE ECHOCARDIOGRAPHY (DE)

In clinical practice, both low- dose and high -dose dobutamine echocardiography (DE) are performed. Low- dose DE allows assessment of changes in contractile function and high-dose DE allows assessment of both contractile reserve and stress-induced myocardial ischemia. For prediction of recovery of regional function, low-dose DE has a sensitivity and specificity of 79 and 78%, with a positive predictive value and negative predictive value of 76 and 82%. High-dose DE has a sensitivity and specificity of 83 and 79%, with a positive and negative predictive values of 73 and 85% respectively. High-dose DE has a significantly higher sensitivity and negative predictive value than low-dose DE [4].

THALLIUM-201 IMAGING (TI-201)

Usually two TI-201 protocols, rest-redistribution and reinjection are used to assess ischemic viable myocardium. The rest-distribution technique has a sensitivity and specificity of 87 and 56% with positive and negative predictive values of 71 and 78% respectively. The TI-201 reinjection protocol has a sensitivity and specificity of 87 and 50% and positive and negative predictive values of 58 and 81%. Thus, TI-201 rest-redistribution appears to have significantly higher specificity and positive predictive value than TI-201 reinjection protocol [4].

TECHNETIUM -99M LABELED AGENTS

The use of technetium-99m labeled agents yields a sensitivity and specificity of 83 and 65%, and a positive and negative predictive value of 74 and 76% respectively. The use of technetium-99m labeled agents without the addition of nitrates yielded a sensitivity and specificity of 83 and 57% and a positive and a negative predictive value of 72 and 71% respectively. With addition of nitrates, the sensitivity and specificity are 81 and 69% and the positive and negative predictive values of 72 and 78%. Nuclear imaging with technetium-99m labeled agents with addition of nitrates appears to have a higher specificity and negative predictive value than without nitrates [4].

18 FLUORODEOXY GLUCOSE POSITRON EMISSION TOMOGRAPHY (FDG PET)

FDG PET imaging studies are increasingly performed for identification of viable myocardium. The sensitivity and specificity of FDG PET are 92 and 63% and positive and negative predictive values of 74 and 87% respectively.

MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance imaging (MRI) is being increasingly used to assess myocardial viability. Resting MRI can be used to determine wall thickness and contractile function at rest. Myocardial segments with an end-diastolic wall thickness <6mm usually indicate transmural scar and the function of these segments do not improve after revascularization. Dobutamine MRI is used to assess contractile reserve. Contrast-enhanced MRI using gadolinium-based contrast agents, permits detection of the extent and transmurality of scar tissue.

MRI using end-diastolic wall thickness appears to have sensitivity and specificity of 95 and 41% and positive and negative predictive values of 56 and 92%. The sensitivity and specificity of dobutamine MRI are 74 and 82% and both positive and negative predictive values 78%. Contrast-enhanced MRI has a sensitivity and specificity of 84 and 63% and positive and negative predictive values of 72 and 78%.

Comparison of these techniques for the prediction of improving the regional function of hibernating myocardial segments suggest that FDG PET has the highest sensitivity followed by TI-201 imaging and technetium-99m labeled agents. In general, nuclear imaging techniques have a higher sensitivity than DE. However, DE appears to have highest specificity. The DE and FDG PET also have the highest positive predictive value. On the other hand, FDG PET has the highest and nuclear imaging with technetium -99m labeled agents lowest negative predictive value.

PREDICTION OF RECOVERY OF GLOBAL SYSTOLIC FUNCTION

It should be emphasized that in different studies using the same technique, and in the studies using different techniques, a wide variety and variable criteria have been used to assess changes in the global left ventricular systolic function.

The DE appears to have an approximate sensitivity and

specificity of 57 and 73%, and positive and negative predictive values of 63 and 68%. The TI-201 imaging studies have a sensitivity and specificity of 84 and 53% and the positive and negative predictive values of 76 and 64% respectively. Only limited studies have been done with the use of technetium - 99m labeled agents to assess changes in left ventricular global function after revascularization. The sensitivity and specificity appear to be 84 and 68% and the positive and the negative predictive values of 74 and 80%. The FDG PET studies have the sensitivity of 83 and 64% with positive and negative predictive values of 68 and 80%. One contrast-enhanced MRI study [5], reported that the greater the amount of dysfunctional myocardium detected, greater is the increase in ejection fraction after revascularization. The comparison of these various imaging modalities appear to have very similar positive and negative predictive values to predict the improvement of global left ventricular function after revascularization [4].

PREDICTION OF IMPROVEMENT OF SYMPTOMS OF HEART FAILURE AND EXERCISE CAPACITY

Only very few studies using these various imaging modalities have investigated and reported changes in heart failure severity after revascularization. In general, in patients with viable myocardium NYHA functional class tends to improve and in absence the functional class does not change [4].

CHANGES IN PROGNOSIS

When DE was used, the patients with viable myocardium undergoing had the best survival rates whereas the highest annualized mortality rates were noted in patients receiving medical therapy or without viable myocardium.

The TI-201 imaging studies have reported that the patients with viable myocardium had the best survival after revascularization whereas the annualized mortality was highest in patients with non viable myocardium. Intermediate mortality rates were observed with medical therapy. Very limited studies are available where technetium-99m labeled agents were used to assess prognosis. In one study, during a follow-up period of 40 months, the annualized mortality rate in patients with viable myocardium was 3% after successful revascularization as compared to 9% in patients who received medical therapy [6]. The FDG PET studies have also reported that in patients with viable myocardium the annualized mortality rates are lowest after revascularization and highest in patients without viable myocardium. The annualized mortality rate is intermediate with medical therapy [4].

It should be appreciated that the results of all these studies reporting change of prognosis after revascularization are based on retrospective analysis. Furthermore, when the results of revascularization have been compared to those of medical therapy, the aggressive treatment for coronary artery disease and left ventricular dysfunction were not available.

Does regional and global left ventricular systolic function, symptoms and prognosis improve after revascularization in patients with left ventricular systolic dysfunction?

That both myocardial metabolic and left ventricular regional and global mechanical function improves after revascularization was reported within a few years of introduction of coronary artery bypass graft surgery [7-9]. In these studies, however, most patients had only mildly or moderately reduced ejection fraction. However, recently more and more patients with markedly reduced ejection fraction are undergoing revascularization. It is therefore relevant to be familiar with the results of revascularization in these patient populations and what factors are likely to be associated with improved prognosis.

In the coronary artery surgery (CASS) registry, there were 651 patients who had ejection fraction of <35%. The five year survival rate was significantly better in surgical patients (68%) compared to patients treated medically (54%). The benefit from surgery was greater in patients with left ventricular ejection fraction of <26%. Five year survival with surgery (63%) was significantly higher than that with medical treatment (43%) [10]. Many studies have been performed since then and reported benefits of revascularization in certain subsets patients with reduced ejection with or without angina and with or without overt heart failure. Various predicting factors have also been proposed to identify patients who are likely to benefit.

In a recent study, it was also reported that operative mortality is related to a number of risk factors. The conventional coronary artery bypass surgery (LVEF 30.1%) and of pump techniques (LVEF 27.5%) have little influence on the mortality but as expected, the morbidity was higher with conventional technique (35.7%) compared to the off pump technique (19.7%). The risk factors were urgency of surgery and comorbidities [11].

It has been previously reported that revascularization is beneficial in patients with low left ventricular ejection fraction whose presenting symptom is angina and it is unlikely to benefit patients present with symptoms of heart failure without angina. However, recent studies have reported that the benefit in terms of improvement of ventricular function and long term prognosis depends on the magnitude of viable myocardium present before revascularization. If the extent of viable myocardium is about 70% of the left ventricle, symptomatic improvement, improvement in ventricular function and prognosis is similar whether the presenting symptom is angina or heart failure, whether revascularization is by coronary artery bypass surgery or by percutaneous intervention. Three years survival of patients with angina and viable myocardium in the angina group was 89% and in the heart failure group 87% [12].

Conclusions. A substantial increase in the understanding of the mechanism of hibernation and its detection has occurred recently. A large number of studies identify the best technique to detect and quantitate the extent of viable ischemic dysfunctioning myocardium, and it appears that nuclear imaging and FDG PET are both useful in clinical practice. Revascularization, whether by coronary artery bypass surgery or by PCI, appears to be effective in relieving symptoms and improving left ventricular function and prognosis even in patients with a very low ejection fraction, provided a sufficient magnitude of viable of myocardium is present. Thus, detection of viable hibernating myocardium is highly desirable before revascularization is undertaken.

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